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EXAMINER	
MOORE, WILLIAM W	

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1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/884,456	HOUGHTON ET AL.	
	Examiner	Art Unit	
	William W. Moore	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response

The amendment to claim 27 made in Response filed 12 October 2005 introduces the ambiguous, and indefinite, transitional phrase "consists essentially of", which requires the statement of a new ground of rejection below under the second paragraph of 35 U.S.C. § 112. However the rejections of record of the claims herein under 35 U.S.C. §§ 101 and 102 stated in the communication mailed 12 April 2005 were made in error and are hereby WITHDRAWN. Although present within a composition, the term "isolated" suffices to distinguish a polynucleotide from an HCV genome within an HCV particle. Applicant's preliminary amendments to the specification filed 19 February 2002 indeed provided sequence identifiers throughout the specification.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 27-44 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 5,371,017 for the reasons set forth at page 4 of the communication mailed 12 April 2005. While Applicant states at page 6 of the Response that a terminal disclaimer will be filed upon an indication of allowable subject matter herein, the rejection must be maintained until and unless an effective terminal disclaimer is filed.

The following is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim 36 remains provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 15 of copending Application No. 10/438,313, which is an application for reissue of U.S. Patent No. 5,371,017 for the reasons stated at page 4 of the communication mailed 12 April 2005. While Applicant states at page 6 of the Response that a terminal disclaimer will be filed upon an indication of allowable subject matter in either application, the rejection must be maintained until and unless an effective terminal disclaimer is filed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27-44 remain rejected for reasons of record under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection of record stated in the communication mailed 12 April 2005 indicates why polynucleotides encoding the regions of the hepatitis C virus polyprotein present in the fusion polypeptides P600, P500, P300 and P190 of the specification's Example 5, cannot encode a protein having a structure sufficient for HCV-specific proteolysis even though these proteins comprise amino acids recognized in the art to be necessary for two separate kinds of HCV-specific proteolyses. The proteins of Example 5 comprise the amino-proximal 155 amino acids of human superoxide dismutase [hSOD] fused to HCV amino acids 946 through 1630 [P600], 946 through 1457 [P500], 946 through 1244 [P300], and 964 through 1144 [P190]. It is agreed that each protein includes the His952 and Cys993 later found to be necessary for NS2/NS3 metalloprotease cleavage. It is

also agreed that the encoded P600, P500, P300 and P190 proteins include the His1083 and Asp1107 necessary for NS3/NS4A serine protease cleavage, and that the encoded P600, P500, P300 proteins, but not the P190 protein, include the Ser1165 necessary for NS3/NS4A serine protease cleavage. The Declaration under 37 CFR 1.132 of Dr. Amy J. Weiner submitted with the Response was considered together with the Applicant's arguments at pages 7-15 of the Response filed 12 October 2005 have been fully considered but the arguments presented are not persuasive. Applicant's concerns in the second paragraph at page 7 of the Response are moot because Pallaoro et al., of record, teach that even a minimal NS2/NS3 metalloprotease, if fused to a heterologous solubilizing peptide, is capable of authentic auto-processing activity when expressed in an *E. coli* host cell.

Applicant's primary argument is that the specification inherently discloses a specific proteolytic activity native to, i.e., authentic to, an HCV polypeptide, the HCV NS2/NS3 metalloprotease's auto-processing cleavage, see pages 7 and 8 of the Response, proposing that the P600 fusion protein having the 686-amino acid sequence of Figure 1 and SEQ ID NO:86 is an adequate written description of a "NS3 domain hepatitis C virus protease or active . . . truncation analog" having a proteolytic activity required of the proteins encoded by polynucleotides comprised by the claimed compositions and vectors: an NS2/NS3 metalloprotease activity. SEQ ID NO:86 and the sequence of Figure 1 correspond to the amino acid sequence of the entire P600 fusion protein and SEQ ID NO:70 represents the HCV amino acid sequence therein. Applicant also points to the 299- and 202-amino acid sequences present within SEQ ID NO:70 that are set forth, respectively, in SEQ IDs NOs:66 and 65, as adequate written descriptions of proteolytically active "truncation analogs" of at least SEQ ID NO:70. Applicant then argues at page 8 of the Response that a peptide substrate for an HCV protease is

disclosed in the specification where Example 5 reports a "specific cleavage with the NS3 domain" region of the P600, P500 and P300 proteins expressed in *E. coli* host cells. Applicant next argues at pages 8-12 of the Response that Example 5 discloses an HCV-specific protease activity because the cleavage products reported in the Example must result from autocatalysis mediated by the subsequently described NCV NS2/NS3 metalloprotease.

Applicant separately argues at pages 12-15 of the Response that Examples 10 and 11 of the specification are a constructively reduced to practice of an NS3 domain protease in view of both disclosures in the specification of the catalytic triad of amino acids in Applicant's HCV isolate - His1083, Asp1107 and Ser1165 - and the publication by Eckart et al., of record, which compares the HCV NS2/3 autocatalytic activity of the protein encoded by their pG3ZYPN plasmid, see Figure 2 at page 403, which the Response indicates, see the footnote at page 13, has 106 further HCV NS2 domain amino acids beyond the amino-terminus of SEQ ID NO:70 and eleven fewer HCV NS3 domain amino acids at the carboxyl-terminus of SEQ ID NO:70, with the HCV NS3/NS4A serine protease activity of proteins encoded by their pG3ZYPS and gG3ZYBB plasmids, see page 404 where Figure 3A illustrates cleavage products of the former and Figure 3B illustrates cleavage products of the latter. Both of the pG3ZYPS and gG3ZYBB plasmids comprise the entire NS3 domain and at least the first 139 amino acids of the NS4 domain, including the entire NS4A region, see the description of coordinates for the latter in the legend for Figure 3B.

As noted in the communication mailed 12 April 2005, the specification defines an HCV NS3 domain protease as having termini established "by **expression and processing in an appropriate host** of a DNA construct **encoding the entire NS3 domain**" [emphasis supplied]. The specification teaches, pages 6-9, that the protease

activity of the NS3 domain is that of a serine protease, identifying the catalytic triad of histidine, aspartate, and serine present in such proteases in Tables 1 and 2, each of which is present in the P600, P500, P300 fusion polypeptides of Example 5 and two of which are present in the P199 fusion polypeptide. Pages 22-23 of the specification further define the disclosure as directed to a serine protease and the specification does not discuss or suggest the activity of an HCV protease other than a serine protease. Applicant acknowledges that the P600, P500, P300, and P199 fusion polypeptides each include the carboxyl-terminal 81 amino acids of an HCV polyprotein NS2 domain, commencing at position 946 of the polyprotein encoded by Applicant's HCV isolate. Applicant also acknowledges that SEQ ID NO:70, corresponding to the HCV polyprotein region in the P600 protein having a carboxyl-terminus at position 1630 of the polyprotein encoded by Applicant's HCV isolate, includes all but the 23 carboxyl terminal amino acids of an HCV NS3 domain. Compare SEQ ID NO:70 with the amino acid sequences of Figure 1 of Choo et al., 1991, made of record herewith, and of Figures 1D through 1E of Houghton et al., US 5,863,719, made of record with the Information Disclosure Statement filed 9 April 2003. Further compare the polypeptide expressed by the pG3ZYPN plasmid described at page 400, second paragraph of Material and Methods, of Eckart et al., made of record with Applicant's Information Disclosure Statement, using the nucleotide sequence positions in Figures 1A through 1G of the '719 patent when numbered from the "-319" position of Figure 1A which corresponds to the "-319" position at the 5' terminus of the nucleotide sequence in Figure 1 of Choo et al., 1991. In addition to the 106-amino acid extension into the HCV NS2 domain and the exclusion of eleven amino acids of the NS3 domain of the P600 protein noted above, the protein encoded by pG3ZYPN plasmid of Eckart et al. differs from the specification's p600

superoxide dismutase region at the amino terminus of the p600 fusion polypeptide with a single, initiating, methionine.

It is agreed that the specification's SEQ IDs NOs:65, 66, 68 and 70, as well as the HCV NS2-NS3 protein encoded by pG3ZYPN plasmid of Eckart et al., all comprise the art-recognized NS2/3 cleavage site at positions 1005 through 1014 of the polyprotein encoded by Applicant's HCV isolate, corresponding to positions 60-69 of SEQ ID NO:70. Compare these amino positions in Figure 1E of the '719 patent with Figure 1 of Reed et al., 1995, of record. It is also agreed that the specification's SEQ IDs NOs:65, 66, 68 and 70, and the HCV NS2-NS3 protein encoded by the pG3ZYPN plasmid of Eckart et al. lack the art-recognized NS3/NS3A protease cleavage sites between the NS3 and NS4 regions and the NS4 and NS5 regions of the HCV polyprotein, and that further divide the NS4 and NS5 regions internally. See Figure 2(c) of Yao et al., 1999, of record. Apart from position taken at pages 12-15 of the Response, Applicant proposes that the specification be construed to disclose a "NS3 domain protease" as having the activity of the NS2/NS3 metalloprotease in cleaving the NS2/NS3 cleavage site between positions 1026 and 1027 of the HCV polyprotein encoded by Applicant's isolate and corresponding to positions 65 and 66 of SEQ ID NO:70. See the C-terminal amino acids of Figure 1 of Pallaoro et al., and see also Figure 2 of Grakoui et al., Figure 1 of Santolini et al., and Table II of Thibeault et al., all of record.

Because Applicant no longer maintains that Example 5 of specification discloses the activity of a serine protease residing within an HCV NS3 domain and instead argues that the specification inherently discloses an HCV polypeptide possessing an authentic, native, HCV proteolytic activity of the NS2/NS3 metalloprotease, the issue of whether the specification provides an adequate written disclosure of the polynucleotides of the claimed compositions and vectors rests on whether the P600, P500, P300 and P190

polypeptides of Example 5 provide enough of the art-recognized structure of an HCV NS2/NS3 metalloprotease to permit cleavage at the art-recognized NS2/NS3 cleavage site **that is present in each of these proteins**. The discoveries of others made after the effective filing date of the instant application, discussed in the following paragraphs A through E, show that the HCV polyprotein amino acid sequence beginning at position 946 and extending through at least position 1144 in the P190 polypeptide, corresponding to the positions 1 through 198 of SEQ IDs NOs:66-68 and 70 and shared by all proteins in Example 5 of the specification, cannot provide a structure sufficient to support the proteolytic activity of an HCV NS2/NS3 metalloprotease. Each paragraph compares findings of publications of record with the amino acid sequences of the P600, P500, P300 and P190 proteins and with the amino acid sequence of the pG3ZYPN-encoded protein [pG3ZYPN protein] of Eckart et al. cited in Applicant's arguments.

A. Hijikata et al., of record, found that "[a]t least the region from residue 898 to 1233 was . . . essential for the detection of [the Zn^{++}-dependent metalloprotease] Cpro-1 activity" in *in vitro* transcription/translation experiments. See page 4673. The P600, P500, P300 and P190 polypeptides each lack the 49-amino acid region between positions 898 and 946 that Hijikata considered sufficient and the P190 polypeptide also lacks the region between HCV polyprotein positions 1144-1233. By way of comparison, the pG3ZYPN-encoded protein has an amino acid sequence that extends from position 840 to position 1619 of an HCV polypeptide, a 106-amino acid amino-proximal extension into the NS2 domain beyond any protein of the specification's Example 5, thus clearly provides a structural basis sufficient for the activity of an HCV NS2/NS3 protease according to Hijikata et al.

B. The amino acid sequence of the pG3ZYPN protein is also similar to the HCV amino acid sequence region that Grakoui et al., of record, found important for the

activity of an HCV NS2/NS3 metalloprotease: "HCV sequences between residues 827-1207 appear required for efficient processing at the 2/3 site in mammalian cells". See page 10584. Grakoui et al. used expression plasmids prepared for another publication, however, thus did not investigate additional amino-terminal truncations on the NS2 domain region corresponding to those made by Hijikata et al. Each of the P600, P500, P300 and P190 polypeptides lacks the N-proximal NS2 domain amino acid region from position 827 through position 946 that Grakoui et al. utilized and the P190 polypeptide lacks the region from positions 1144-1207 employed by Grakoui et al. The report of Reed et al., of record, agrees with those of Grakoui et al., see page 4134, but Reed et al. likewise made no amino-terminal truncations that corresponds to those of Hijikata et al., using instead for comparison an HCV NS2/NS3 protein extending from position 936 through position 1039 defective in metalloprotease activity.

C. Santolini et al., of record, determined, that the "N-terminal boundary of the NS2 portion (of the NS2/NS3 metalloprotease) . . . appears to be located between (positions) 849 and 923", while the "C-terminal boundary of the NS3 portion . . . appears to be located between positions 1137 and 1237". See page 7463. A related group of investigators, Pieroni et al., of record, considered, page 6376, "that the minimal region of the HCV BK (isolate) precursor required for processing at the NS2-3 site extends from aa 849 to 1237." While the P600, P500, P300 and P190 polypeptides all lack the 23-amino acid region of the minimal NS2 domain between positions 923 and 946 that Santolini et al. and Pieroni et al. found was sufficient for NS2/NS3 metalloprotease activity, all have carboxyl termini extending beyond the minimum region commencing at position 1137 that Santolini et al. and Pieroni et al. found to be sufficient in the HCV NS3 domain. As before, the amino acid sequence of the pG3ZYPN protein extends from the HCV polyprotein position 840 through its position 1619, providing a structural

basis sufficient for the activity of an HCV NS2/NS3 metalloprotease according to Santolini et al. and Pieroni et al.

D. Pallaoro et al., of record, made a series of critical truncations within the NS2 domain region of an HCV NS2/NS3 protease, which they considered to more likely be a bi-molecular cysteine protease rather than a metalloprotease, and found that segments having amino termini at either position 903 or position 907 within an HCV polyprotein NS2 domain, and sharing a carboxyl terminus at position 1026 in an HCV polyprotein NS3 domain, were active auto-processing NS2/NS3 proteases, see Figure 1 at page 9941, whether they were expressed in a cell-free *in vitro* transcription/translation system or as a solubilized fusion polypeptide in an *E. coli* host cell. But Pallaoro et al. found that segments having amino termini at either of positions 913 or 918 in the NS2 domain, but also having a carboxyl terminus at position 1026 in the NS3 domain, had no activity. Most significantly, and a discovery not considered by Applicant's arguments at pages 10-11 of the Response, Pallaoro et al. found that their truncations show that "the (alpha-)helix (region) predicted to exist between residues 915 and 928" was structurally insufficient for protease activity even though they had initially considered it "the first structurally and/or functionally important segment." Instead, the portion of the NS2 domain that provided protease activity, whether expressed as a fusion polypeptide or as an unique HCV protein, was the region that is "immediately after the last predicted transmembrane segment", i.e., including at least position 907 of an HCV polyprotein. See page 9941 at top of left column and Figure 1's legend. The pG3ZYPN protein has an amino acid sequence that extends from position 840 through position 1619 of an HCV polypeptide, clearly providing a structural basis for HCV NS2/NS3 metalloprotease activity according to the discoveries of Pallaoro et al. where it includes the region that Pallaoro found to be sufficient for protease activity, but the P600, P500, P300 and P190

polypeptides all lack the 39-amino acid NS2 domain region between positions 907 and 946 that Pallaoro et al. found sufficient for protease activity even though all but the P190 polypeptide have carboxyl termini extending beyond the minimum region ending at position 1206 that Pallaoro et al. considered to be sufficient in the NS3 domain of an HCV polypeptide.

E. Thibeault et al., of record, determined that a segment of an HCV polyprotein having an amino terminus at position 904, within the same NS2 region immediately after the last predicted transmembrane segment that Pallaoro found to be sufficient for protease activity, and a carboxyl terminus at position 1026 within the NS3 domain, was fully active as an auto-processing protease. Again, the amino acid sequence of the pG3ZYPN protein provides a structural basis that is sufficient for HCV NS2/NS3 protease activity according to Thibeault et al. but the P600, P500, P300 and P190 polypeptides all lack the 42-amino acid NS2 domain region between the polyprotein positions 904 and 946 that Thibeault et al. found sufficient for NS2/NS3 protease activity, even though all but the P190 protein have carboxyl termini beyond the minimum region ending at position 1206, within the NS3 domain, Thibeault et al. found sufficient for NS2/NS3 protease activity.

There can be no agreement with Applicant's arguments at pages 5 through 13 of the Response that the specification inherently discloses the activity of an HCV NS2/NS3 metalloprotease and inherently discloses a peptide substrate for an HCV protease, an auto-processing NS2/NS3 metalloprotease, in view of the fact that each of the P600, P500, P300 and P190 fusion polypeptides lack the regions of the HCV NS2 domain found by Hijikata et al., Grakoui et al., Reed et al., Santolini et al., Pieroni et al., Pallaoro et al. and Thibeault et al. to be required for the authentic auto-processing activity of the HCV NS2/NS3 domain metalloprotease. These findings by the diverse groups of

artisans cited above who investigated the NS2 and NS3 regions of the HCV polyprotein to determine which portions therein are sufficient for auto-processing cleavage activity of NS2/NS3 metalloproteases all show that the specification provides no adequate written disclosure of an HCV NS3 protease, an NS2/NS3 metalloprotease, or any other HCV protease, encoded by a polynucleotide comprised by a claimed composition or vector. Where the specification fails to disclose or teach the structure of the portion of HCV polyprotein sufficient for cleavage at the NS2-NS3 boundary, no "truncation analogs" thereof can adequately be disclosed.

Similarly, there can be no agreement with Applicant's arguments at pages 12 to 15 of the Response that the publication of Eckart et al. supports a constructive reduction to practice of an NS3 domain serine protease that either "comprises" or "consists of" SEQ ID NO:65 in Examples 10 and 11 of the specification. This is because the various proteins expressed with the pG3ZYPS and gG3ZYBB plasmids of Eckart et al., whether or not the Ser1165Gly mutation is present, share the entire NS3 domain and all of the NS4A region of the NS4 domain, structural regions subsequently determined by others to be sufficient for cleaving at the NS3-NS4 boundary. None of the proteins disclosed in the specification possess either the NS3 domain region adjacent to the NS3-NS4 boundary or the NS4 region adjacent to NS3-NS4 boundary.

In view of the fact that each of the P600, P500, P300 and P190 fusion polypeptides lack the regions of the HCV NS2 domain found by Hijikata et al., Grakoui et al., Reed et al., Santolini et al., Pieroni et al., Pallaoro et al. and Thibeault et al. to be required for the authentic auto-processing activity of the HCV NS2/NS3 domain metalloprotease, there can be no agreement with Applicant's arguments at pages 7 through 12 of the Response that the specification adequately discloses the inherent activity of an HCV NS2/NS3 metalloprotease required by proteins encoded by polynucleotides of the

compositions and vectors claimed herein, and that it inherently discloses a peptide substrate for an HCV protease, an auto-processing NS2/NS3 metalloprotease. These findings by the diverse groups of artisans cited above who investigated the NS2 and NS3 regions of the HCV polyprotein to determine which portions therein are sufficient for the auto-processing cleavage activity of NS2/NS3 metalloproteases all show that the specification provides no adequate written disclosure of an HCV NS3 protease, an NS2/NS3 metalloprotease, or any other HCV protease, encoded by a polynucleotide comprised by a claimed composition or vector. Where the specification fails to disclose or teach the structure of the portion of HCV polyprotein, sufficient for cleavage at the NS2-NS3 boundary, no "truncation analogs" thereof can adequately be disclosed.

Similarly, there can be no agreement with Applicant's arguments at pages 13 and 14 of the Response that the publication of Eckart et al. supports a constructive reduction to practice of an NS3 domain serine protease that either "comprises" or "consists of" SEQ ID NO:65 in Examples 10 and 11 of the specification. This is because the various proteins expressed with the pG3ZYPS and gG3ZYBB plasmids of Eckart et al., whether or not the Ser1165Gly mutation is present, share the entire NS3 domain and all of the NS4A region of the NS4 domain, structural regions subsequently determined by others to be sufficient for cleaving at the NS3-NS4 boundary. None of the proteins disclosed in the specification possess either the NS3 domain region adjacent to the NS3-NS4 boundary or the NS4 region adjacent to NS3-NS4 boundary.

The specification provides no independent basis for concluding that a cleavage occurred at the art-recognized HCV NS2/NS3 metalloprotease cleavage site between positions 1026 and 1027 present in each of the P600, P500, P300 and P190 proteins where the calculated molecular mass, 24.9 kD, of a cleavage product consisting of the 155 amino acids of hSOD fused to the 81 HCV NS2 domain amino acids at positions 1-

236 of SEQ ID NO:86 up to the metalloprotease cleavage site is clearly much less than the 34 kD relative molecular mass reported in the specification. See pages 19 and 20 below with an EXPASY pI/MW tool calculation [http://ca.expasy.org/tools/pi_tool.html]. The Federal Circuit has said that a sufficient written description of a genus of biologically active molecules may be achieved by disclosure of a representative number of such molecules defined by their sequence structure by or recitations of structural features common to members of the genus, which features constitute a substantial portion of the genus. Where no disclosed embodiment constitutes an adequate written description of proteins encoded by polynucleotides comprised by claimed compositions and vectors, the diverse, undisclosed, species that "comprise" an NS3 domain or truncation analogs thereof also are not supported by an adequate written description. The rejection of record, based on the disclosures of those in the art whose work is most closely associated with the mechanism proposed by Applicant, is therefore maintained.

Claims 29, 30, 34, 35, 39 and 40 remain rejected for reasons of record under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection of record stated in the communication mailed 12 April 2005 indicates why the regions of the hepatitis C virus polyprotein present in the fusion polypeptides P600, P500, P300 and P190 of the specification's Example 5 are insufficient for HCV-specific proteolysis and why the claims 29, 30, 34, 35, 39 and 40 that describe genera of polynucleotides encoding proteases comprising either SEQ ID NO:63 or SEQ ID NO:64 are unsupported by an adequate written description. Applicant's arguments in the Response filed 12 October 2005, i.e., that SEQ ID NO:63 comprises the histidine necessary for HCV NS3 serine protease proteolytic activity and that SEQ ID NO:64 comprises the serine necessary for HCV NS3 serine protease proteolytic activity, have

been fully considered but they are not persuasive. The facts Applicant argues are not in dispute, yet the specification fails to disclose, discuss, suggest, or teach those further features of a fragment of an HCV polyprotein sufficient for the NS2/NS3 protease activity that Applicant proposes as a basis for the claims' description of polynucleotides comprised by the claimed compositions and vectors. This is because the structural features of SEQ IDs NOs:63 and 64 are insufficient to provide a protein with NS2/NS3 protease activity, just as are the features of the more extensive P600, P500, P300 and P190 proteins all of which comprise both SEQ IDs NOs:63 and 64, are insufficient to provide a protein with NS2/NS3 protease activity for the reasons set forth above. The Federal Circuit has said that a sufficient written description of a genus of biologically active molecules may be achieved by disclosure of a representative number of such molecules defined by their sequence structure by or recitations of structural features common to members of the genus, which features constitute a substantial portion of the genus. Similarly, an adequate written description of a genus of proteins may be achieved by disclosure of a representative number of proteins defined by amino acid sequence or a recitation of structural features common to members of the genus, which features constitute genus. Because no genera of proteolytically active proteins having the separate regions of a serine protease present in either of SEQ IDs NOs:63 or 64 are disclosed, the rejection of record is therefore maintained.

Claims 27-44 remain rejected for reasons of record under 35 U.S.C. § 112, first paragraph, because the specification does not reasonably provide enablement for preparing polynucleotides comprised by the claimed compositions and vectors that encode a protein, including the P600, P500, P300 or P190 proteins, that has an HCV-specific protease activity, or generic versions thereof, or active truncation analogs thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicant's arguments at pages 15 and 16 of the Response filed 12 October 2005 that Examples 4 and 5 of the specification disclose "the structure and activity of a[n

HCV] NS2/3 protease", and that the specification provides a "constructive reduction to practice" and "the structure" of an HCV NS3 serine protease, have been fully considered but they are not persuasive. As indicated in the rejection of record stated in the communication mailed 12 April 2005, the NS2 and NS3 domain regions present in the disclosed P600, P500, P300 and P190 proteins Applicant proposes to be sufficient for HCV NS2/NS3 protease activity have been shown by the subsequent discoveries of others, cited hereinabove and in the rejection of record, to actually be insufficient for HCV NS2/NS3 protease activity. Thus the specification provides no guidance for the preparation of polynucleotides comprised by claimed compositions or vectors encoding proteins that cleave the art-recognized NS2-NS3 cleavage site present in all of the P600, P500, P300 and P190 proteins by virtue of an authentic HCV metalloprotease activity. While the specification identifies a region within the NS3 domain of an HCV polyprotein having the sequence characteristics of a serine protease, i.e., the amino acid sequence set forth in SEQ ID NO:65, and points to analogies between this region and serine proteases located in similar regions of polyproteins encoded by flavivirus genomes, it provides no guidance for preparing polynucleotides comprised by claimed compositions or vectors encoding proteins that cleave the art-recognized NS3-NS4 cleavage site because this site is absent from the P600, P500, P300 and P190 proteins. The rejection of record is therefore maintained.

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 27-44 remain rejected for reasons of record under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant's arguments filed 12 October 2005 have been fully considered but they are not persuasive. At pages 16 and 17 of the Response, Applicant argues limitations that are not present in the claims in pointing to pages 3, 6, and 7 of the specification.

Claim 1 currently recites, "an NS3 domain hepatitis C virus **protease or an active . . . truncation analog**" (emphasis supplied), but no sequence identifier is present in claim 1 with which it can be determined where truncation might begin to define the analogs that "comprise" the peptides of SEQ IDs NOs:63 and 64 of claims 29, 30, 34, 35, 39 and 40, or that "comprise" the larger 202-amino acid sequence identical in both of SEQ IDs NOs:1 and 65 of claims 28, 31, 36, and 41. There is no indication in the specification permitting the public and one of ordinary skill in the art to distinguish a "domain" from "an active truncation analog" of proteins encoded by polynucleotides comprised by the compositions and vectors of the independent claims 27, 32, and 37, from proteins encoded by polynucleotides comprised by compositions and vectors of the dependent claims 28-31, 33-36, and 38-44 because the specification has no structural description of the metes and bounds of a NS3 domain protease distinguishable from a "truncation analog". The public and the artisan seeking to establish the scope of the claimed subject matter cannot determine what is more than a "domain", thus excluded by the claim, from what is less than a "domain" and at the same time a truncation analog of the claim. The issue presented by these claims is the lack of a definite description of the intended subject matter and the rejection of record is maintained.

A new ground of rejection is necessitated by Applicant's amendment of claim 27 in the Response and claims 27-31 are rejected as indefinite because claim 27 recites the phrase, "consisting essentially of", which is ambiguous and indefinite because the claim is intended to describe a polymer wherein each nucleotide is covalently bonded to at least one other nucleotide, and a single covalently-bound molecule has no physically separate, lesser, component, thus cannot "consist essentially of" one component. A molecule of the claim is unlike a composition of matter having at least two components wherein one component is dominant, a subject matter properly described by reciting "consisting essentially of". Claims 28-31 are included in the rejection because they do

not resolve the ambiguity of claim 27 from which they depend. Appropriate transitional terms for describing the intended polymer subject matter are, e.g., "comprises", "has", and "consists of" and since the rejections prompting the choice of the phrase, "consisting essentially of", are now withdrawn, amending the claim to again state "comprising" will overcome this new ground of rejection.

Conclusion

Applicant's amendment necessitated the new ground of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 571.272.0933 and whose FAX number is 571.273.0933. The examiner can normally be reached Monday through Friday between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisory Primary Examiner, Dr. Kathleen Kerr, can be reached at 571.272.0931. The official FAX number for all communications for the organization where this application or proceeding is assigned is 571.273.8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571.272.1600.

William W. Moore
6 January 2006

NASHAAT T. NASHED PHD.
PRIMARY EXAMINER